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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Norman Nashed

Serial No. 09/619,493 : Examiner: S. Qazi

Filed: July 19, 2000 : Group Art Unit: 1616

Title: **THERAPEUTIC GESTAGENS FOR THE TREATMENT OF PREMENSTRUAL DYSPHORIC DISORDER**

DECLARATION UNDER 37 C.F.R. §1.132

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Marie L. Foegh, being duly warned declared that:

I am a citizen of the United States, residing at 44 Adams Drive, Cresskill, NJ.

I possess the degrees of M.D. and D.Sc., having studied at University of Copenhagen Medical School, Copenhagen Denmark. I did postgraduate training at University Hospitals and the University Department OB/GYN at Frederiksberg Hospital in Copenhagen, Denmark. I also held a fellowship in the Department of Medicine at Georgetown University Medical Center, Washington, D.C.

I am currently Vice President of Female Healthcare in Clinical Research at Berlex Laboratories in Montville, NJ.

The following multicenter, double blind, randomized, placebo-controlled, crossover study, evaluating the efficacy and safety of DRSP 3 mg/EE 20 μg (as β-CDC) in treating the symptoms of PMDD has been performed. A total of 511 women were screened and 64 women were randomized into the treatment phase.

Present psychiatric disorders (major depressive disorder, anxiety disorder [panic, obsessive-compulsive, posttraumatic stress], eating disorders, drug and/or alcohol disorders, bipolar I disorder, psychotic disorders, and somatoform disorder) were excluded by the Structured Clinical Interview for DSM-IV (SCID). Subjects were historically screened for PMDD according to DSM-IV criteria for PMDD:

Patients who met the DSM-IV criteria as well as other historical inclusion criteria for the study, and for whom exclusion criteria were absent, were eligible for the Qualification Phase. Diaries were used for recording daily ratings of PMDD symptoms using the Daily Record of Severity of Problems (DRSP) scale starting on the first day of their next menstrual cycle.

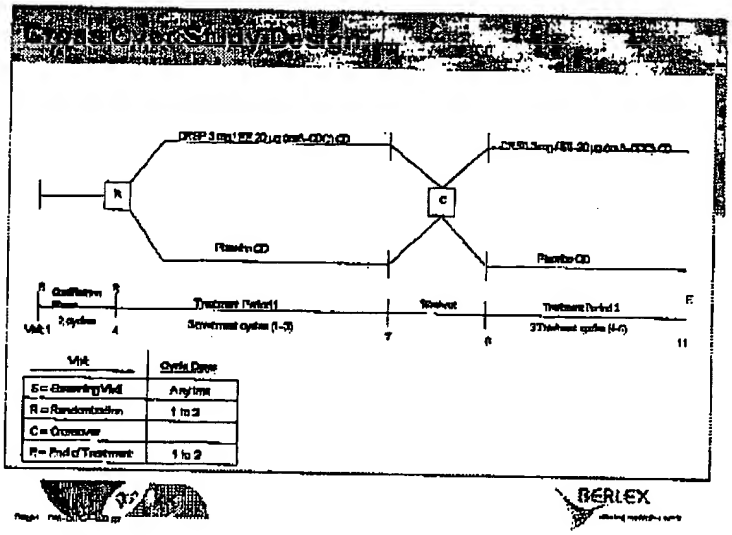
The Qualification Phase included 2 observational cycles: run-in Cycle 1 and run-in Cycle 2. Eligibility for the Treatment Phase was based on the DRSP scale[1] scores during each of the 2 run-in cycles.

Women who were eligible for the study after the Qualification Phase were randomized to a 3-cycle treatment period with either DRSP 3 mg/EE 20 µg (as β-CDC) or placebo. At the conclusion of the first 3 treatment cycles (period 1; treatment cycles 1 through 3), the patients entered a 1 cycle washout interval, after which they crossed over to another 3-cycle treatment with placebo or DRSP 3 mg/EE 20 µg (as β-CDC) (period 2; treatment cycles 4 through 6), the converse of the first treatment group assignment.

The incidence and severity of PMDD symptoms was assessed by evaluation of the daily DRSP-scale scores. The primary endpoint of the study was the change in the average of the last 5 days of the luteal phase of the treatment cycles, compared with the average of the last 5 days of the luteal phase of the two baseline placebo run-in cycles. This endpoint was compared between treatment and placebo groups.

[1] a. Endicott, et al, Premenstrual Changes: Patterns and Correlates of Daily Ratings, J Affective Disorders 1986; 10:127-35 U.S.C § (34) b. Yonkers et al, Symptomatic Improvement of Premenstrual Dysphoric Disorder with Sertraline Treatment, JAMA 1997; 278:983-88 (12) c. Cohen et al, Premenstrual daily Fluoxetine for Premenstrual Dysphoric Disorder: A Placebo-controlled, Clinical Trial Using Computerized Diaries, Obstet & Gunecol 2002; 100:435-43 (3) d. Steiner et al, Fluoxetine in the Treatment of Premenstrual Dysphoria. Canadian Fluoxetine/Premenstrual Dysphoria Collaborative Study Group, NEJM 1995, 8;332:1529-34 (23).

Study design



The primary efficacy variable:

The DRSP-scale (Daily Record of Severity of Problems) – luteal phase total DRSP score based on 21 of the 24 items.

The secondary efficacy variable:

- Three functional impairment items in DRSP (1. Productivity at work, home or school. 2. Interference with hobbies or social activities. 3. Interference with relationship).
- CGI[2] (Clinical Global Improvement, by investigator and patient).
- SF-36[3].
- Endicott Q-LES-Q Questionnaire (short version)[4].
- PMTS Scale (Premenstrual Tension Syndrome Scale)[5].

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[2] CGI: Guy W. ECDEU Assessment Manual for Psychopharmacology. Revised 1st Edition. U.S. Dept Health, Education and Welfare, 1976.

[3] a. Ware, J.E. and Kosinski, M. SF-36 Physical & Mental Health Summary Scales: A Manual for Users of Version 1.Second Edition, Lincoln, RI: QualityMetric Incorporated, 2001; b. Ware, J.E. Jr., Kosinski, M., and Gandek, B., SF-36 Health Survey: Manual & Interpretation Guide, Lincoln, RI: QualityMetric, Inc., 1993, 2000; c. Ware, J.E., Kosinski, M., and Dewey, J.E., How to Score Version 2 of the SF-36 Health Survey, Lincoln, RI: QualityMetric, Inc., 2000.

[4] Endicott, J, Nee J., Harrison W., Blumenthal R. Quality of Life Enjoyment and Satisfaction Questionnaire: A New Measure. Psychopharmacol Bull 1993;29:321-326.

[5] A. Steiner et al, Premenstrual Tension Syndrome: The Development of Research Diagnostic Criteria and New Rating Scales, Acta Psychiatr, Scand. 1980, 62:177-80 (38). B. Steiner, et al, The Measurement of Premenstrual Mood Symptoms, 1999, J. Affect Disord 53: 269-273 (3).

- **Results**

Demographics

Variable	Statistics/Class	DRSP/EE, Placebo	Placebo, DRSP/EE
Age (years)	N	34	30
	MEAN	31.9	31.8
	SD	4.7	6.4
Ethnic Group	Caucasian	23	25
	Black	4	3
	Hispanic	3	2
	Asian	1	0
	Other	3	0
BMI	Mean	26.0 ± 5.5	26.7 ± 4.8
Number Pregnancies	Mean	2.2 ± 1.8	2.2 ± 2.0
Cycle Average Length (Days)	MEAN	29.4 ± 2.1	28.2 ± 1.9
	SD	2.06	1.86
Smoker	No	30	28
	Yes	4	2

Conclusion

The study showed a highly significant treatment effect on PMDD of DRSP 3 mg +ethinyl estradiol 20 ug administered in 24/28 days cycles. The efficacy is demonstrated for all 24 items in the DRSP instrument as well within each category of symptoms. This significant effect was demonstrated across all instruments applied in the study, and can be seen in the Appendix.

The effect size of DRSP + E2 on the symptoms associated with PMDD exceeds that seen with the placebo using the same and similar instruments.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

April 21, 2004
Date

Dr. Marie L. Foegh

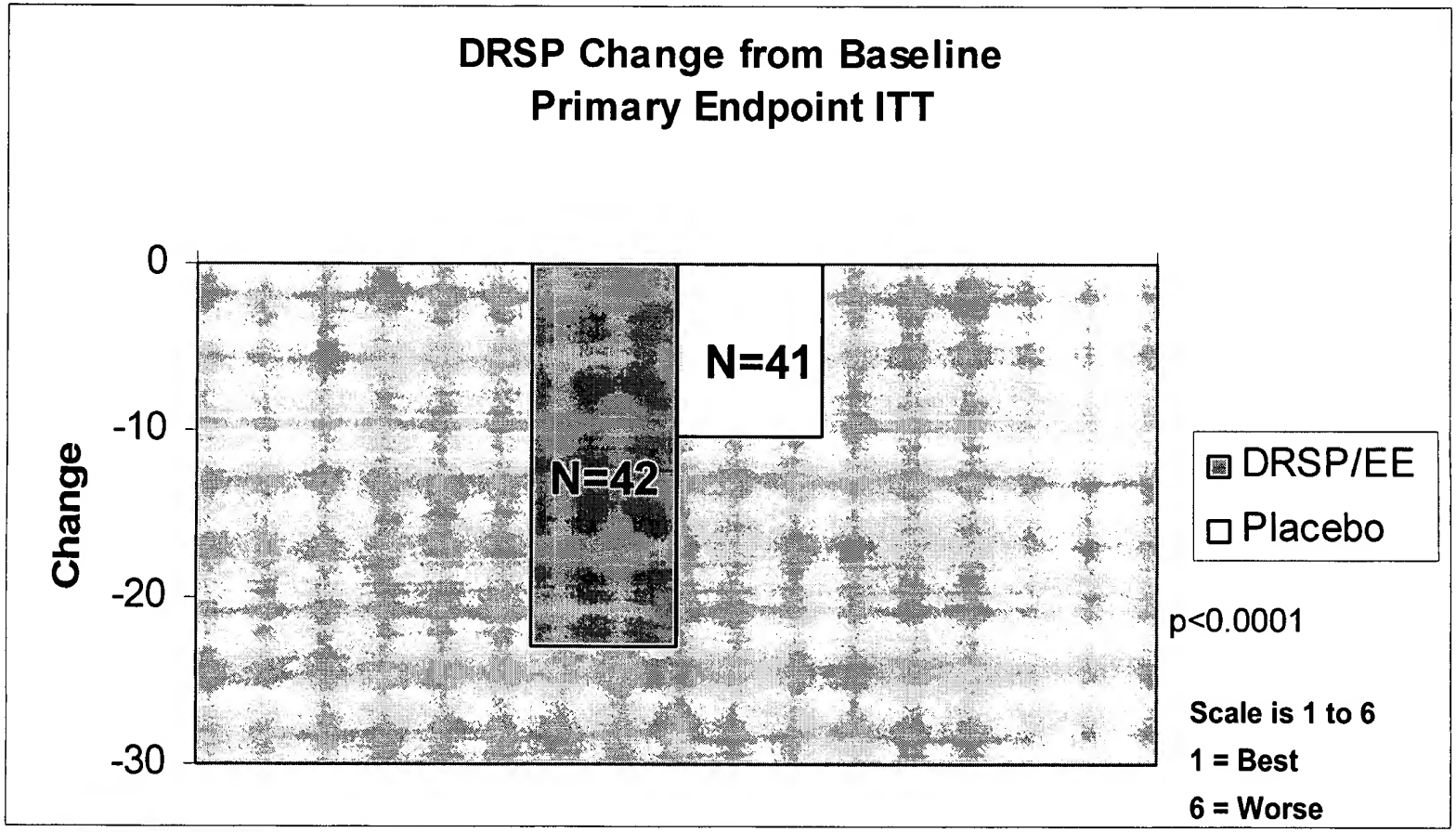
PMDD Instruments

		ITEMS	FREQUENCY	SELF	INVESTIGATOR
Primary	DRSP	24	DAILY	X	
Secondary	CGI	1 PATIENT 3 INVESTIGATOR	X4	X	X
	SF-36	36	X3	X	
	PMTS	35 PATIENT 10 INVESTIGATOR	X3	X	X
	Q-LES-Q	15	X3	X	

DRSP Inclusion Criteria
Scale 1-6

- **The following must be fulfilled in each of the two consecutive baseline cycles:**
  - → **5 distinct items with no overlap**
  - → **Luteal phase daily average ≥ 3.0 (at least one item must represent a non-physical symptom)**
  - → **Follicular phase daily average ≤ 2.5 for all non-physical item**
  - → **Late luteal phase daily average ≥ 2 times follicular phase daily average for 3 of the 5 distinct items without overlap (at least one item must represent a non-physical symptom)**
  - → **For ≥ 2 luteal days, functional impairment questions score ≥ 3 on ≥ 1 of 3 impairment items**

Daily Record of Severity of Problems (DRSP)



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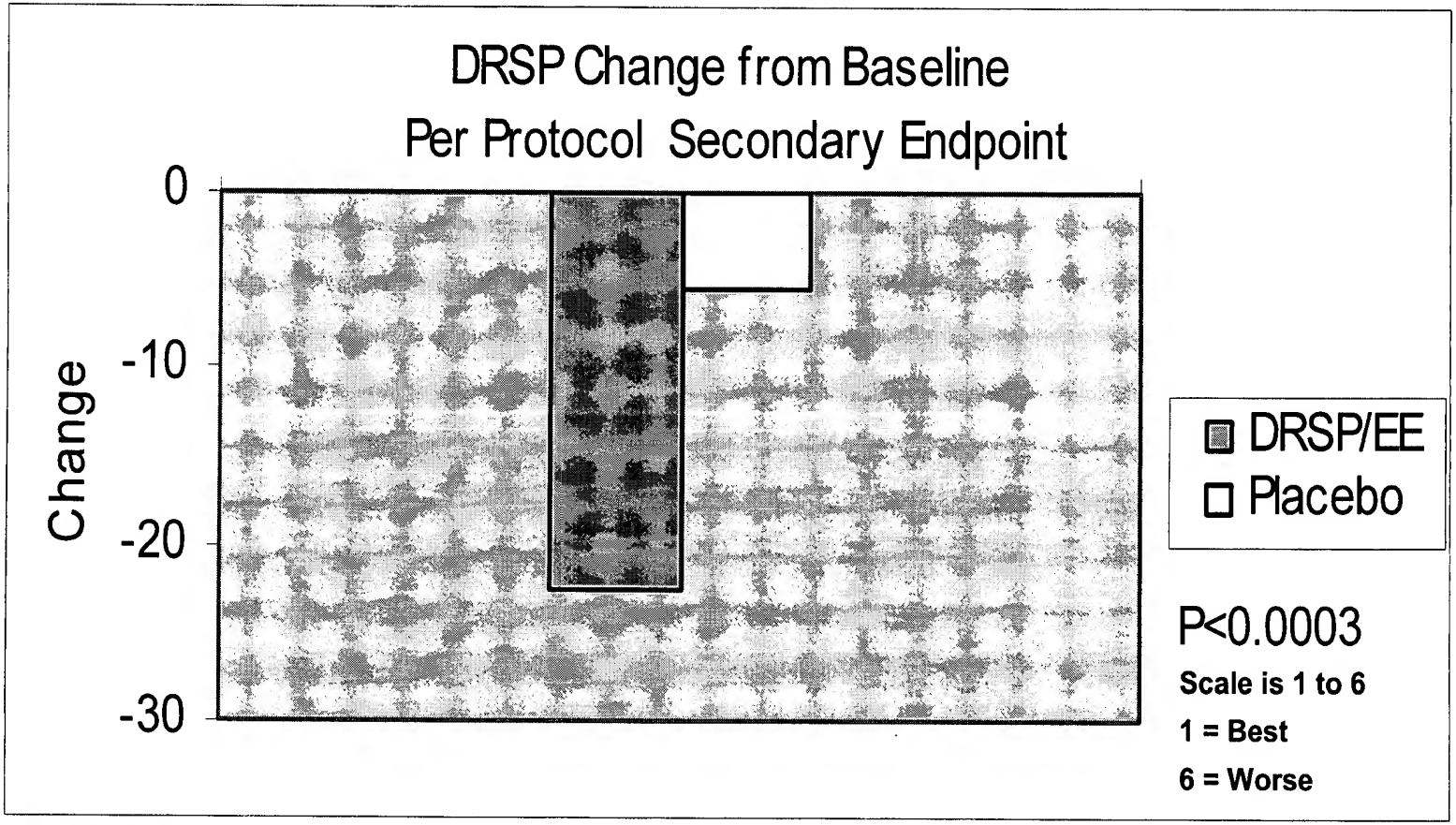
Daily Record of Severity of Problems



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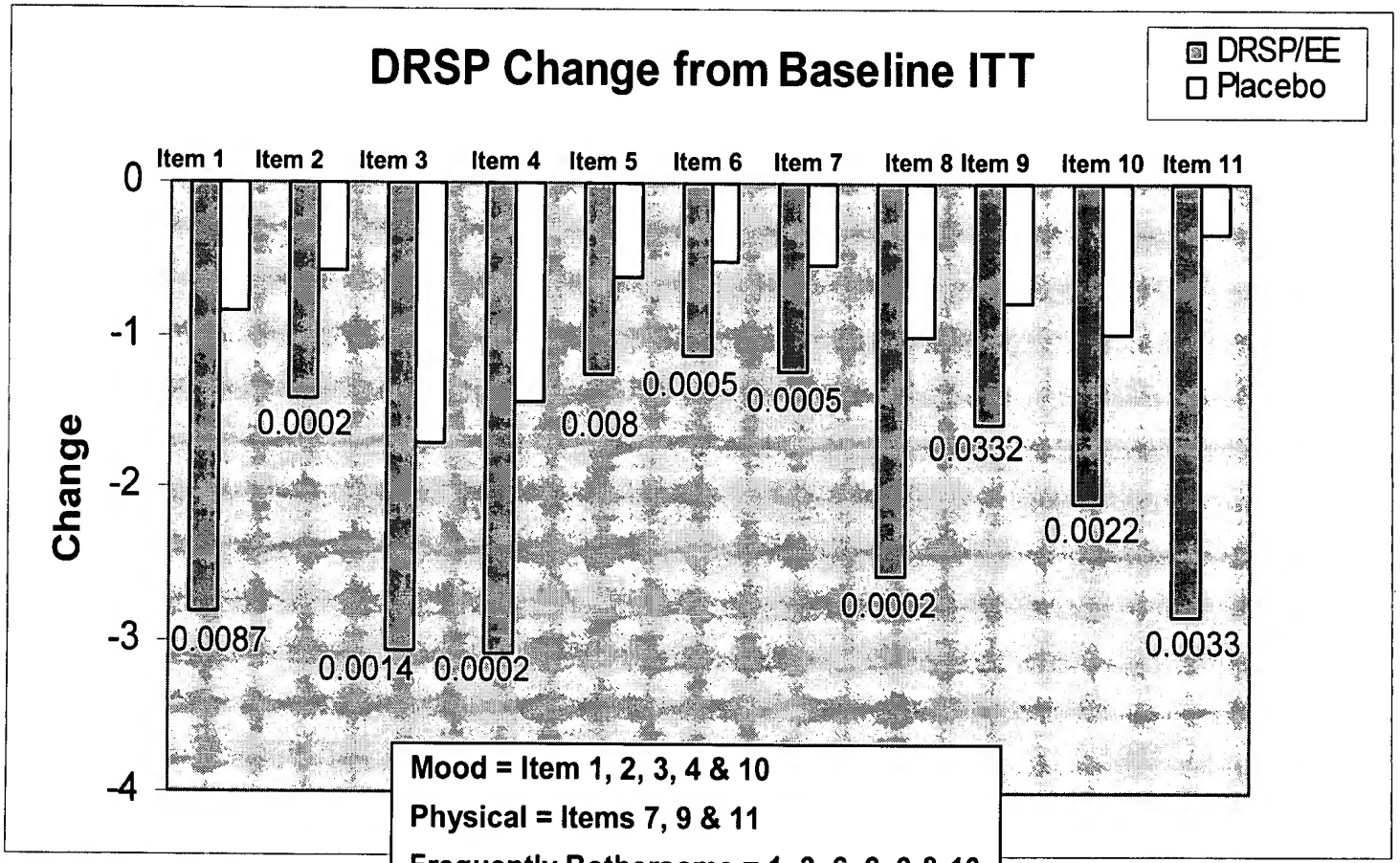
Daily Record of Severity of Problems



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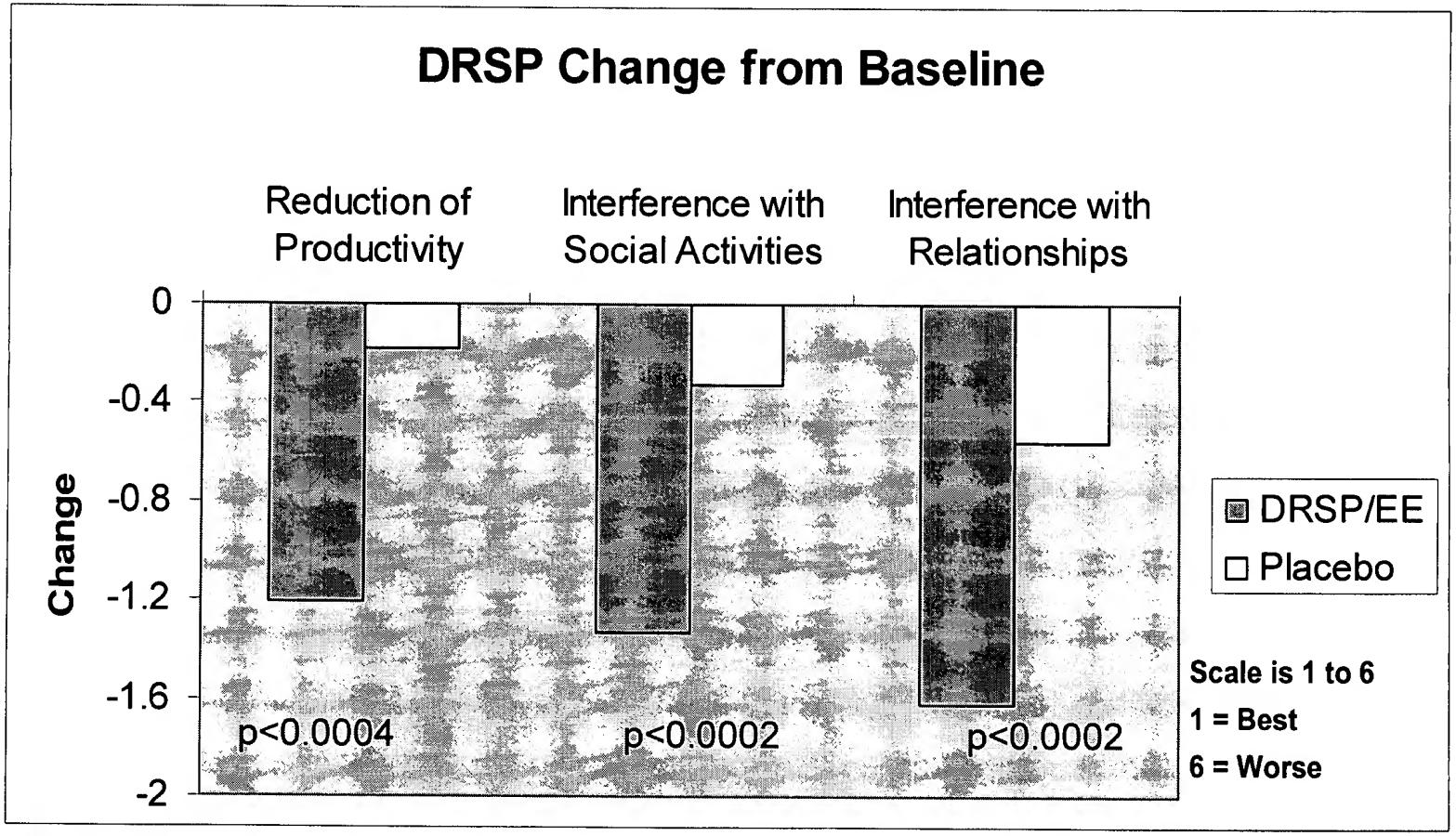
Daily Record of Severity of Problems



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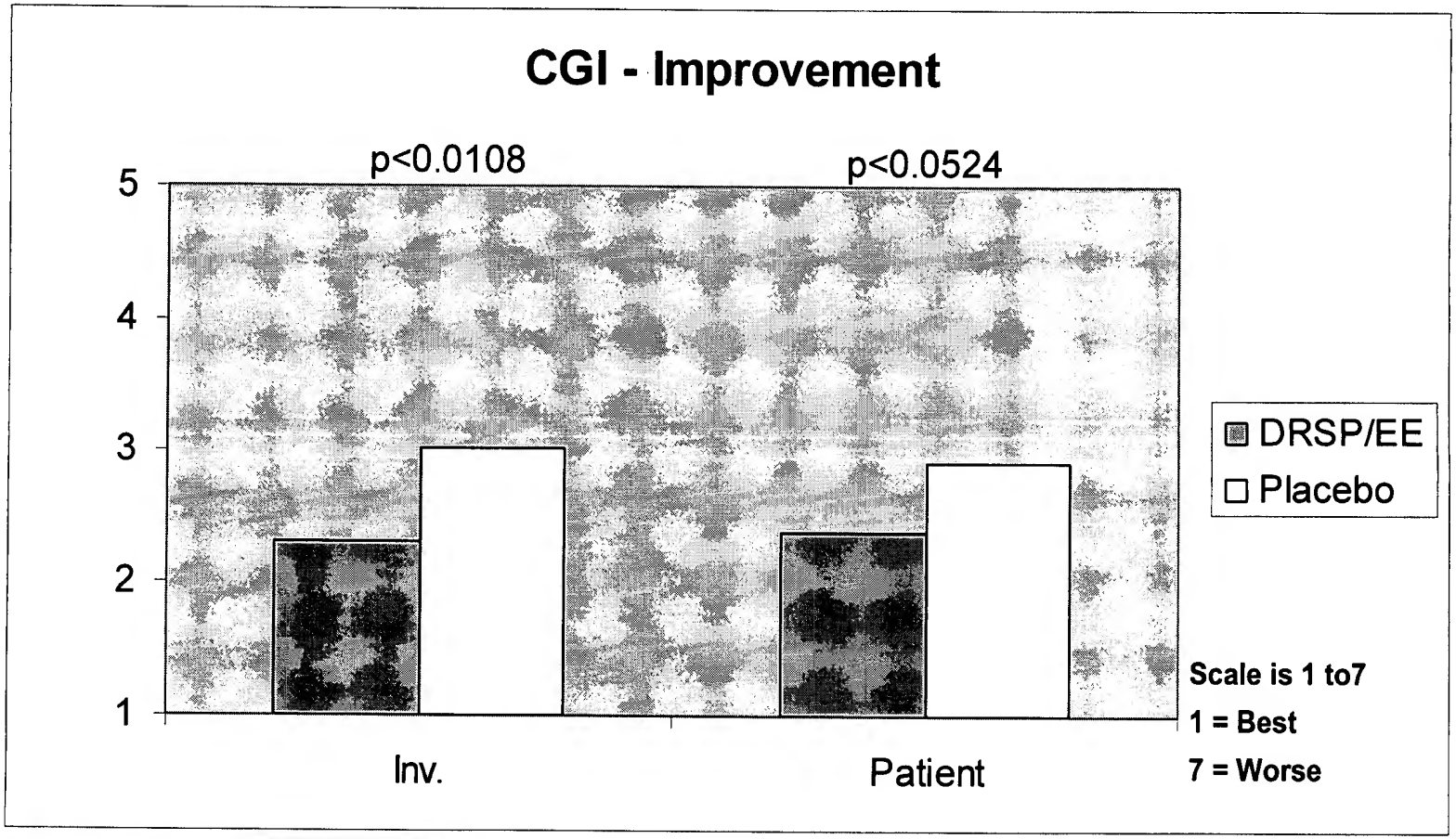
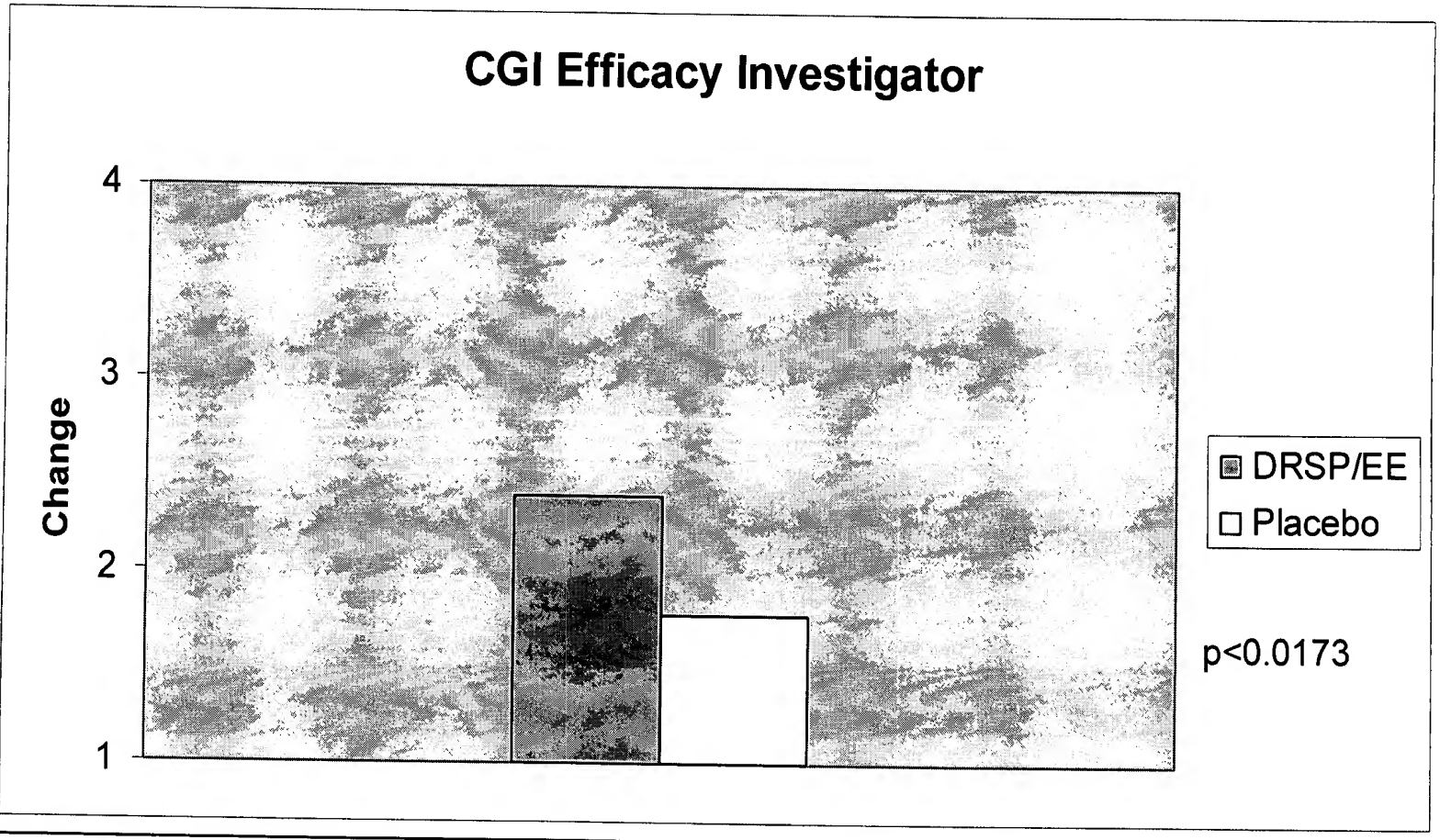
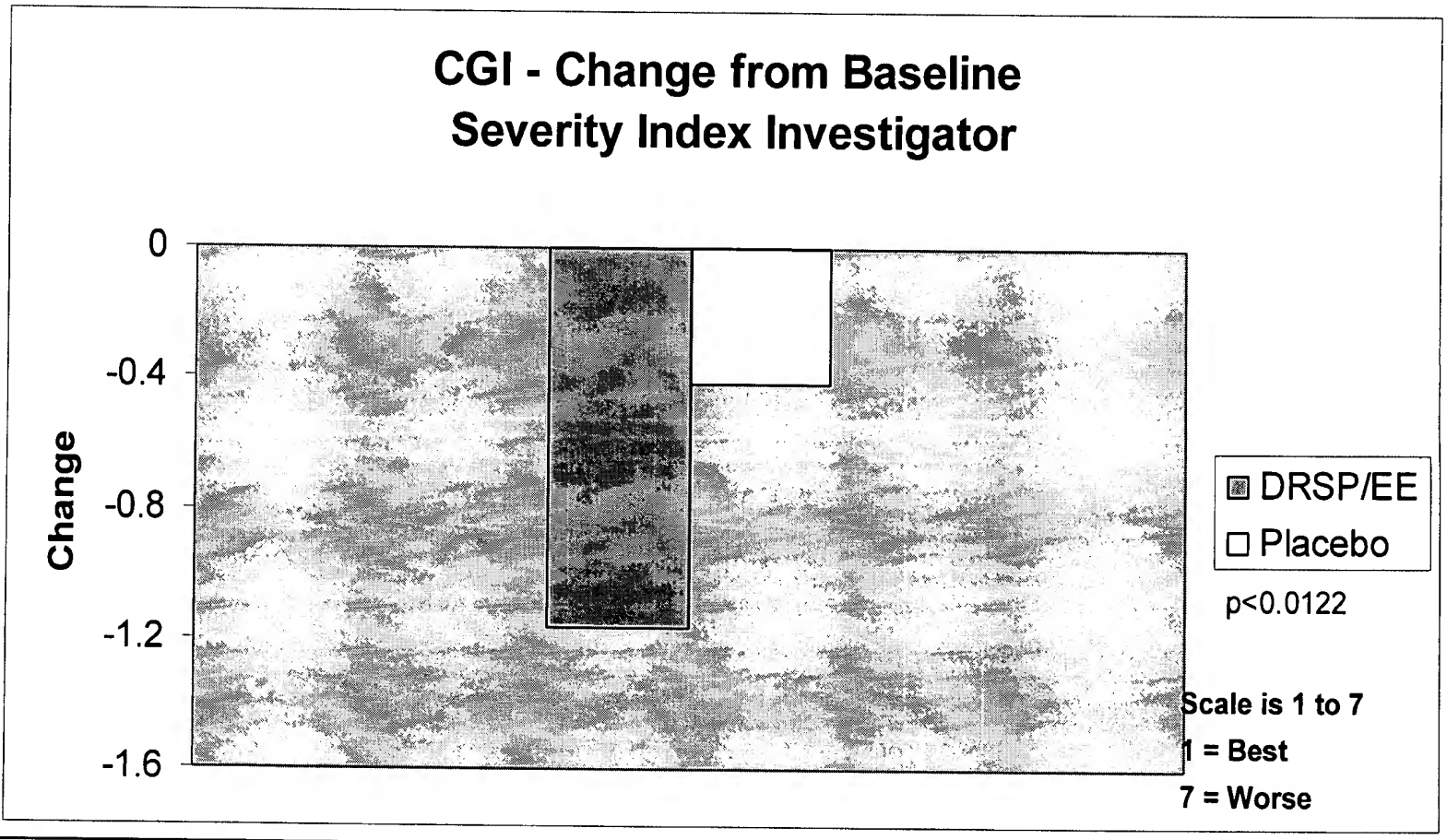
Clinical Global Impressions (CGI)



Clinical Global Impressions



Clinical Global Impressions

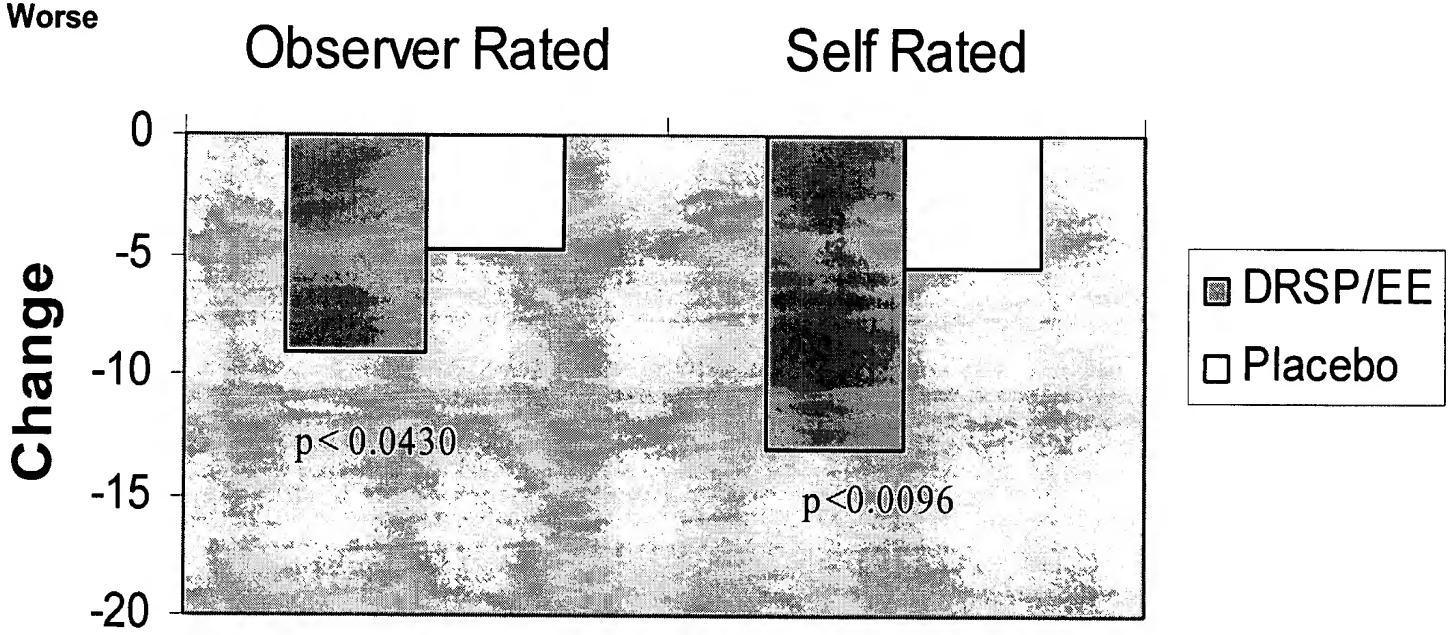


Pre-Menstrual Tension Syndrome (PMTS)

Observer Rated = 10 Items
Scale = 0 to 4
0 = Best
4 = Worse

PMTS Change from Baseline
ITT

Self Rated =
36 Items of yes / no



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Quality of Life Questionnaire (Q-LES-Q)